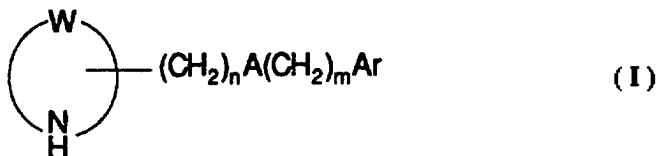




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(21) International Application Number: PCT/EP93/03473 (22) International Filing Date: 7 December 1993 (07.12.93) (30) Priority Data: 9226111.4 15 December 1992 (15.12.92) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): BROWN, Thomas, Henry [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldhar- bour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). COOPER, David, Gwyn [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Lane, The Pinnacles, Harlow, Essex CM19 5AD (GB). (74) Agent: FLORENCE, Julia, A.; Corporate Intellectual Property, SmithKline Beecham, Mundells, Welwyn Garden City, Herts AL7 1EY (GB).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: USE OF ARYLOXYALKYL SUBSTITUTED CYCLIC AMINES AS CALCIUM CHANNEL ANTAGONISTS AND NEW PHENYLOXYALKYL PIPERIDIN DERIVATIVES (57) Abstract Use of a compound of formula (I), in which W is $-(CH_2)_4$, $(CH_2)_5$, $-(CH_2)_2O(CH_2)_2$ or $-(CH_2)_2S(CH_2)_2$, n is 0 to 6; m is 0 to 3; A is a bond, $-CH=CH-$, $-C=C-$, oxygen, sulphur or NR^1 ; R^1 is hydrogen, C_1 -alkyl or phenyl C_1 -alkyl; and Ar is aryl or heteroaryl, each of which may be optionally substituted; or a pharmaceutically acceptable salt thereof as a therapeutic agent. Certain novel compounds of formula (I) and processes for preparing them are also described.		



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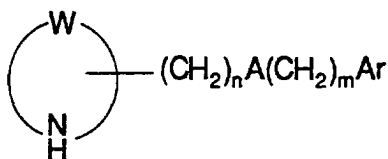
USE OF ARYLOXYALKYL SUBSTITUTED CYCLIC AMINES AS CALCIUM CHANNEL ANTAGONISTS AND NEW PHENYLOXYALKYL PIPERIDIN DERIVATIVES

The present invention relates to cyclic secondary amine derivatives, processes for their preparation, pharmaceutical compositions containing them and their use in therapy.

International Applications No's WO92/02501, WO92/02502, WO92/22527 and WO93/15052 describe various tertiary nitrogen-containing heterocyclic compounds, which compounds are said to have activity as calcium blocking agents. Corresponding secondary amines are described as potential intermediates.

We have now found that certain of these compounds and other secondary cyclic amine derivatives exhibit therapeutic activity in particular as calcium channel antagonists.

The present invention therefore provides, in a first aspect, the use of a compound of formula (I):



Formula (I)

in which

W is $-(\text{CH}_2)_4$, $(\text{CH}_2)_5$, $-(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$ or $-(\text{CH}_2)_2\text{S}(\text{CH}_2)_2$

n is 0 to 6;

m is 0 to 3;

A is a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, oxygen, sulphur or NR^1 ;

R^1 is hydrogen, C_{1-8} alkyl or phenyl C_{1-4} alkyl; and

Ar is aryl or heteroaryl, each of which may be optionally substituted; or a pharmaceutically acceptable salt thereof as a therapeutic agent.

Compounds of formula (I) and their pharmaceutically acceptable salts may for example be used in the treatment of disorders wherein a calcium channel antagonist is indicated.

In the compounds of formula (I) W preferably represents $(\text{CH}_2)_4$ or $(\text{CH}_2)_5$.

The group $-(\text{CH}_2)_n\text{A}(\text{CH}_2)_m\text{Ar}$ may be substituted on any carbon atom in the ring. When W is $(\text{CH}_2)_4$ or $(\text{CH}_2)_5$ the substituent is preferably α to the ring nitrogen atom.

The values of n, m and A should be chosen such that the chain $(\text{CH}_2)_n\text{A}(\text{CH}_2)_m$ contains at least one atom. In general, the length of the chain $-(\text{CH}_2)_n\text{A}(\text{CH}_2)_m$ is from 2 to 6 atoms. Preferred values for n and m depend on the group A. Thus for example when A is oxygen the sum of n+m is from 1 to 5; for example n may be 1 or 2 and m may be zero.

A is preferably oxygen or a bond.

When Ar represents aryl, suitable groups include, for example, unsaturated monocyclic and unsaturated or partially saturated bicyclic and tricyclic ring systems of up to 15 carbon atoms, such as, for example, phenyl, naphthyl, tetrahydronaphthyl, fluorene, fluorenone, dibenzosuberene and dibenzosuberone. Preferred are optionally substituted phenyl rings.

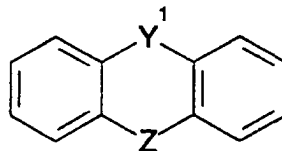
An aryl group may be substituted, for example, by a C₁₋₂alkylenedioxy group (e.g. phenyl substituted by a 3,4-methylenedioxy group) or by 1 to 3 substituents selected from halogen, C₁₋₄alkoxy, nitro, SC₁₋₄alkyl, NR^{2a}R^{2b} (in which R^{2a} and R^{2b} independently represent H or C₁₋₄alkyl), OCF₃, C₁₋₆alkyl, trifluoromethyl, CN, optionally substituted phenyl, optionally substituted phenoxy, optionally substituted benzoyl, optionally substituted phenylC₁₋₄alkyl and optionally substituted phenylC₁₋₄alkoxy.

Suitable optionally substituted phenylC₁₋₄alkyl groups include, for example benzyl. Suitable optionally substituted phenylC₁₋₄alkoxy groups include, for example benzyloxy groups.

Suitable substituents for said optionally substituted phenyl, phenoxy, benzoyl, phenylC₁₋₄alkyl and phenylC₁₋₄alkoxy groups include for example halogen, C₁₋₄alkyl, C₁₋₄alkoxy, nitro and trifluoromethyl groups.

Preferably the aryl group is a phenyl ring substituted by one or two substituents, in particular, by a phenyl, phenyl(C₁₋₄)alkyl, phenoxy, benzoyl or phenylC₁₋₄alkoxy group; or by two chloro atoms especially in the 3- and 4-positions of the phenyl ring.

When Ar represents heteroaryl suitable groups include, for example, unsaturated or partially saturated bicyclic and tricyclic ring systems containing at least one heteroatom. A bicyclic ring system preferably contains 8 to 10 ring members, such as quinolinyl and tetrahydroquinolinyl. A tricyclic ring system preferably contains from 11 to 14 ring members, and most preferably has the structure :



wherein Y¹ represents Y(CH₂)_r, Y is O, S or NR³ (where R³ is hydrogen or C₁₋₄alkyl), Z is (CH₂)_q or -CH=CH-, q is 0, 1 or 2 and r is 0 or 1, or is a corresponding dehydro ring system. Examples of tricyclic heteroaryl groups include dibenzofuranyl, dibenzothienyl, carbazole, N-methylcarbazole, acridine and dibenzoxepine. The heteroaryl ring can be linked to the remainder of formula (I) via any suitable ring atom.

Suitable substituents for said heteroaryl rings include, for example, 1 to 3 substituents selected from halogen, trifluoromethyl, C₁₋₄alkyl and C₁₋₄alkoxy.

Alkyl groups present in the compounds of formula (I), alone or as part of another group, can be straight or branched. Thus a C₁₋₆alkyl group may be for example methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl or any branched isomer thereof such as *iso*-propyl, *tert*-butyl or *sec*-pentyl.

5 Particularly preferred compounds of formula (I) for use according to the present invention are those wherein W is (CH₂)₅, the substituent -(CH₂)_nA(CH₂)_mAr is α to the ring nitrogen atom, A is oxygen, n is 1 or 2, m is zero and Ar is phenyl substituted by one of benzyl, benzoyl, phenoxy or benzyloxy, or by two chloro atoms, or Ar is dibenzofuranyl.

10 It will be appreciated that for use in medicine a salt of a compound (I) should be pharmaceutically acceptable. Examples of pharmaceutically acceptable salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, methanesulphonate or similar pharmaceutically acceptable inorganic or organic acid addition salts. Other non-
15 pharmaceutically acceptable salts, such as oxalates, may be used for example in the isolation of final products and are included within the scope of this invention.

It will be appreciated that the compounds of formula (I) may contain one or more asymmetric centres. Such compounds will exist as optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of
20 the two are included within the scope of the invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention. In addition, when A represents -CH=CH- the compounds will exist as geometric isomers, and the invention encompasses the use of all such isomers and mixtures thereof.

Compounds of formula (I) wherein W is -(CH₂)₄ and the group
25 -(CH₂)_nA(CH₂)_mAr is α to the pyrrolidine nitrogen atom are novel compounds and as such form a further aspect of the invention. Preferably A is oxygen, n is 1 or 2 and m is zero. Preferred values of Ar are as defined above.

Compounds of formula (I) wherein Ar represents phenyl substituted by benzoyl are also novel compounds and form a yet further aspect of the invention. A particularly
30 preferred group of compounds wherein Ar represents benzoylphenyl is that in which W is (CH₂)₅, A is oxygen, n is 1 or 2 and m is zero. Most preferably the substituent -(CH₂)_nA(CH₂)_mAr is α to the ring nitrogen atom.

Particular compounds for use according to the invention include:

- 2-[2-(4-benzyloxyphenoxy)ethyl]piperidine,
- 35 2-[2-(4-phenoxyphenoxy)ethyl]piperidine,
- 2-[2-(2-benzylphenoxy)ethyl]piperidine,
- 4-[2-(3,4-dichlorophenoxy)ethyl]piperidine,
- 4-[2-(4-benzyloxyphenoxy)ethyl]piperidine,

- 4-[2-(4-benzylphenoxy)ethyl]piperidine,
 3-(4-benzoyloxyphenoxymethyl)piperidine,
 3-(4-benzylphenoxyethyl)piperidine,
 2-[4-benzylphenoxyethyl]piperidine,
 5 2-[4-benzoyloxyphenoxymethyl]piperidine,
 (S)-2-[4-benzylphenoxyethyl]pyrrolidine,
 2-[2-(3-benzoylphenoxy)ethyl]piperidine,
 2-[2-(4-benzoylphenoxy)ethyl]piperidine,
 (+)-2-(2-[4-benzylphenoxy]ethyl)piperidine,
 10 (-)-2-(2-[4-benzylphenoxy]ethyl)piperidine,
 and salts thereof.

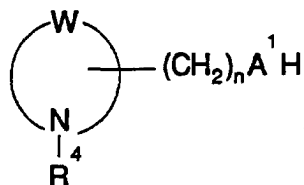
The above are also novel compounds and form a yet further aspect of the invention.

Other preferred compounds for use according to the present invention include :

- 15 2-[2-(2-dibenzofuranyloxy)ethyl]piperidine,
 2-[2-(3,4-dichlorophenoxy)ethyl]piperidine,
 2-[2-(4-benzylphenoxy)ethyl]piperidine, and salts thereof.

The compounds for use according to the present invention can be prepared by processes analogous to those known in the art, for example the general methods described
 20 in WO92/02501, WO92/02502, WO92/22527 and WO93/15052. Thus, a compound of formula (I) may be prepared by a process which comprises:

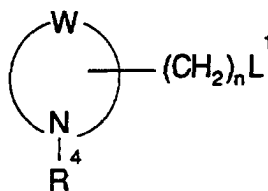
(a) for compounds of formula (I) in which A is O, S or NR¹, reaction of a compound of formula (II):



25 **Formula (II)**

in which W and n are as described for formula (I), A¹ is O, S or NR¹, and R⁴ is an N-protecting group with a compound of formula L(CH₂)_mAr in which m and Ar are as described for formula (I), and L is a leaving group;

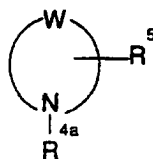
(b) for compounds of formula (I) in which A is O, S or NR¹, reaction of a
 30 compound of formula (III):



Formula (III)

in which W, n and R⁴ are as described above and L¹ is a group displaceable by a nucleophile, with a compound of formula HA¹(CH₂)_mAr where m and Ar are as described for formula (I) and A¹ is as described for formula (II); or

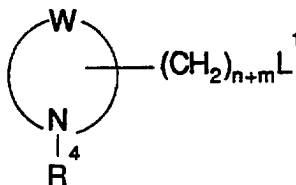
(c) for compounds of formula (I) in which A is NR¹, reduction of a compound of formula (IV) :



Formula (IV)

10 in which R⁵ represents the group
 -(CH₂)_nN(R¹)C(O)(CH₂)_{m-1}Ar or -(CH₂)_{n-1}C(O)N(R¹)(CH₂)_mAr,
 R^{4a} is hydrogen or an N-protecting group, and W, n, m, and Ar are as described above.

(d) for compounds of formula (I) in which A is a bond, reaction of a compound of formula (V) :

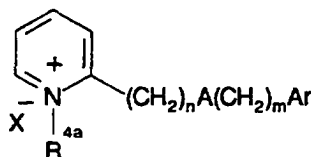


Formula (V)

(wherein W, R⁴, L¹, m and n are as hereinbefore defined);

with a compound of formula X¹Ar in which Ar is as described for formula (I), and X¹ is an alkali metal;

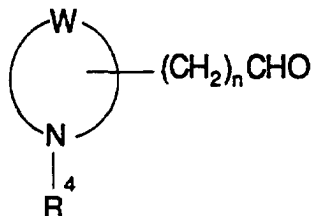
20 (e) For compounds where W is (CH₂)₅ and A is O, S, NR¹ or a bond, reduction of a compound of formula (VI):



Formula (VI)

wherein A, Ar m and n are as hereinbefore defined, R^{4a} is hydrogen or an N-protecting group and X⁻ is a counter ion;

(f) For compounds wherein A is -CH=CH-, reaction of a compound of formula (VII) :



Formula (VII)

(wherein W, R⁴ and n are as hereinbefore defined) with a reagent serving to introduce the group Ar;

(g) Interconversion of one compound of formula (I) to a different compound of formula (I), e.g. the reduction of a compound wherein A is -CH=CH- to a compound wherein A is -CH₂-CH₂-, or reduction of a benzoyl substituent on the group Ar to a benzyl group; followed where necessary by removal of the N-protecting group R⁴, and optionally thereafter forming a salt.

In a further aspect the present invention also provides a process for preparing a novel compound of formula (I) e.g a compound of formula (I) wherein W is -(CH₂)₄ and the group -(CH₂)_nA(CH₂)_mAr is α to the pyrrolidine nitrogen atom, or a compound as specifically named above, which process comprises any of processes (a) to (g) described above, as appropriate, followed where necessary by removal of the N-protecting group R⁴, and optionally thereafter forming a salt. Those skilled in the art will readily be able to determine which specific processes will be applicable to the preparation of a given compound.

In process (a) the reaction between a compound of formula (II) and a compound L(CH₂)_mAr can take place under conditions which depend on the nature of the group L and the value of m. For example, when L is halogen or a sulphonic acid residue such as a tosylate or mesylate and m is other than zero, the reaction is carried out under standard conditions in a solvent, optionally in the presence of a base. When a fluoro-substituted aryl compound F-Ar is employed in process (a) (to prepare compounds where m is zero), the reaction is effected in the presence of a strong base such as sodium hydride, and in an inert organic solvent such as DMSO or dimethylformamide.

The reaction between a compound of formula (III) and a compound of formula HA¹(CH₂)_mAr (process b) can take place under conditions which depend on the nature of L¹ and A. For example when L¹ is hydroxy, m is 0 and A¹ is oxygen or sulphur the reaction is carried out in the presence of diethyl azodicarboxylate and triphenyl phosphine.

Such a reaction is known as the Mitsunobu reaction (as described in Synthesis 1981, 1). Alternatively the leaving group L^1 may be for example a halogen atom or a sulphonyloxy group eg. methane-sulphonyloxy or p-toluene sulphonyloxy. In this case the reaction may be effected in the presence or absence of solvent and at temperature in the range 0 to 200°C.

The reduction of a compound of formula (IV) according to process (c) can be effected by methods known in the art, for example using a reducing agent such as lithium aluminium hydride. Conveniently a compound of formula (IV) can be prepared (for example as described below) and reduced in a 'one-pot' reaction, without isolation of compound (IV) itself.

The reaction between a compound of formula (V) and a compound of formula X^1Ar in process (d) can take place under standard conditions known to those skilled in the art for the formation of carbon-carbon bonds.

Reduction of a compound of formula (VI) according to process (e) may be effected for example by hydrogenation, using a noble metal catalyst such as platinum, palladium or platinum oxide, suitably in a solvent such as an alcohol eg. ethanol.

Process (f) may be effected using a Wadsworth-Emmons reagent of the formula $Ar(CH_2)_{m+1}P(O)(OAlk)_2$, such as a diethylphosphonate, or a Wittig reagent of the formula $Ar(CH_2)_{m+1}PPh_3X^-$ (where X^- is an anion) which compounds are available commercially or can be prepared by known methods. The reaction may be carried out in a solvent such as tetrahydrofuran optionally containing a crown ether such as 15-crown-5 or 18-crown-6, and in the presence of a strong base such as sodium hydride, or potassium tert-butoxide.

Interconversion reactions according to process (g) may be effected by methods well known in the art. Thus for example conversion of a compound (I) wherein A represents $-CH=CH-$ into a compound (I) wherein A represents $-CH_2-CH_2-$ may be effected by catalytic reduction and reduction of a benzoyl substituent to benzyl may be carried out using a reducing agent such as sodium borohydride in trifluoroacetic acid.

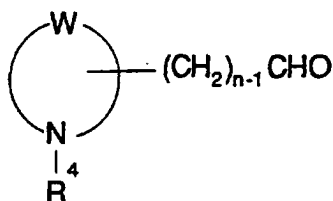
Protecting groups R^4 include lower alkyl groups such as methyl; aralkyl groups such as benzyl, diphenylmethyl or triphenylmethyl; and acyl groups such as acetyl, trifluoroacetyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, tert-butyloxycarbonyl or benzyloxycarbonyl. In process (e) a protecting group R^{4a} is preferably alkyl e.g. methyl or aralkyl e.g. benzyl. Such groups may be removed by methods which are well known in the art. An alkyl group such as methyl may be removed by treatment with a haloalkyl haloformate such as 1-chloromethylchloroformate, aralkyl group such as benzyl may be cleaved by hydrogenolysis, and an acyl group such as benzoyl may be cleaved by hydrolysis. It will be appreciated that a protecting group R^4 or R^{4a} present in any of the above compounds (II) to (VII) as well as compounds (VIII) below should be chosen such

that it will not be cleaved by or participate in any of the reactions that the particular compound is intended to undergo, and furthermore such that its removal will not disturb any other groups or moieties present in the molecule. Such factors can be readily ascertained by those skilled in the art, to whom appropriate protecting groups will thus be readily apparent.

Compounds of formula (II) can be prepared from the corresponding compounds in which R^4 is hydrogen, by methods well known in the art. For example an acyl group may be introduced by reaction with an appropriate acid derivative such as an acid chloride or anhydride, or an activated ester, e.g. an alkyldicarbonate such as di-tert-butylidicarbonate or a haloformate such as ethylchloroformate.

The corresponding compounds of formula (II) in which R^4 is hydrogen are available commercially, known in the literature or can be prepared by standard techniques; for example by reduction of the corresponding 2-hydroxy-alkylpyridine.

Alternatively, the compounds of formula (II) in which A^1 is oxygen can be prepared by reduction of a compound of formula (VIII):



Formula (VIII)

in which R^4 and n are as hereinbefore described. In this instance R^4 should be a group such as alkyl, which is not cleaved by reductive conditions.

Compounds of formula (III) wherein L^1 is OH can be prepared as described for compounds of formula (II), and compounds of formula (III) wherein L^1 is a halogen atom, or a mesyloxy or tosyloxy group can be prepared from the corresponding alcohol in conventional manner.

Compounds of formula (IV) wherein R^5 is a group $-(CH_2)_nN(R^1)C(O)(CH_2)_{m-1}Ar$ can be prepared by reacting a compound of formula (II) wherein A^1 represents NR^1 with an acylating agent corresponding to the group $-(CH_2)_mAr$, for example an acid chloride $ClOC(CH_2)_{m-1}Ar$.

Compounds of formula (IV) wherein R^5 is a group $-(CH_2)_{n-1}C(O)N(R^1)(CH_2)_mAr$ may be prepared for example by reaction of a corresponding compound wherein R^5 represents $-(CH_2)_{n-1}CO_2H$ or an activated derivative thereof such as an acid halide, ester or anhydride, with an amine of formula $HN(R^1)(CH_2)_mAr$. It will be appreciated that when the acid itself is employed, reaction with the amine should be effected in the presence of a coupling agent. The carboxylic acid

may itself be prepared for example by oxidation of the corresponding alcohol, ie. a compound of formula (II) wherein A¹ is oxygen.

Compounds of formula (V) may be prepared in analogous manner to compounds of formula (III); where necessary the chain length may be increased using methods well
5 known in the art.

A compound of formula (VI) may be prepared using the general methods described in processes (a) to (d) above.

Compounds of formula (VII) may be prepared by conventional methods, for example the oxidation of a compound of formula (II) wherein A¹ is oxygen, or conversion
10 of the corresponding ester, e.g. by reaction with thionyl chloride and N,O-dimethylhydroxylamine hydrochloride, to give the N-methyl-N-methoxycarboxamide, which can be reduced to the aldehyde using diisobutylaluminium hydride. Compounds of formula (VII) wherein n is 1 may be prepared from the corresponding compound wherein n is zero by various methods. For example the aldehyde wherein n is
15 zero may be treated with (methoxymethyl) triphenylphosphonium chloride and potassium t-butoxide, followed by a strong acid, e.g. concentrated sulphuric acid, resulting in the aldehyde wherein n is 1. Alternatively the aldehyde may be converted to the corresponding cyanomethyl derivative as described in EPA 363085 followed by acid hydrolysis, conversion to the N-methyl-N-methoxycarboxamide and reduction. These
20 procedures may also be used to form higher homologues.

When a compound of formula (I) is obtained as a mixture of enantiomers, these may be separated by conventional methods such as crystallisation in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column. Suitable resolving agents include optically active acids such as R-(-)- or S-(+)-mandelic acid.

25 Compounds of formula (I) have been found to exhibit calcium influx blocking activity for example in neurons. As such the compounds are expected to be of use in therapy in treating conditions and diseases related to an accumulation of calcium in the brain cells of mammals, in particular humans. For example, the compounds are expected to be of use in the treatment of anoxia, ischaemia including for example stroke, migraine, visceral pain, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative
30 diseases such as Alzheimer's disease and age-related memory disorders; mood disorders and drug addiction withdrawal such as ethanol addiction withdrawal.

The invention therefore provides the use of a compound of formula (I) in the manufacture of a medicament for the treatment of disorders where a calcium channel
35 antagonist is indicated. Thus for example a compound of formula (I) or a pharmaceutically acceptable salt thereof may be used in the manufacture of a medicament for the treatment of a condition or disease related to (e.g. caused or exacerbated by) the

accumulation of calcium in the brain cells of a mammal e.g a human, such as for example, any of the aforementioned conditions.

In a further aspect of the invention there is also provided a method of treatment of a condition or disease caused or exacerbated by the accumulation of calcium in the brain cells of a mammal which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof. Thus, for example, the present invention provides a method of treatment of anoxia, ischaemia including for example stroke, migraine, epilepsy, traumatic head injury, AIDS-related dementia, neurodegenerative diseases such as Alzheimer's disease and age-related memory disorders, and drug addiction withdrawal such as ethanol addiction withdrawal, which comprises administering to a subject in need thereof, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

For use in medicine, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

The compounds of the invention may be administered by any convenient method for example by oral, parenteral, buccal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

The compounds of formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Compounds of the invention may also be administered parenterally, by bolus injection or continuous infusion. Typical parenteral compositions consist of a solution or

suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

5 Both liquid and solid compositions may contain other excipients known in the pharmaceutical art, such as a cyclodextrin or a solubilising agent such as Cremophor.

Preferably the composition is in unit dose form such as a tablet, capsule or ampoule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg
10 (and for parenteral administration contains preferably from 0.1 to 60 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, eg. 5 to 200 mg or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg,
15 preferably between 0.1 mg and 60 mg, eg. 1 to 40 mg of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Alternatively the compounds of the invention may be administered by continuous intravenous infusion, preferably at a dose of up to 400mg per day. Thus, the total daily dosage by oral administration will be in the range 1
20 to 2000 mg and the total daily dosage by parenteral administration will be in the range 0.1 to 400 mg. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

BIOLOGICAL DATA

Ca^{2+} current was measured *in vitro* using cell preparations of sensory neurons
25 from dorsal root ganglia as described in WO92/02501 and WO92/02502.

Compounds of Example 1-18 gave percentage inhibition of plateau Ca^{2+} current in the range 48 to 97% @ 20 μM of test compound.

Pharmaceutical Formulations

The following represent typical pharmaceutical formulations according to the present
30 invention, which may be prepared using standard methods.

IV Infusion

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
35 Solvent/complexing agent	to 100 ml

Bolus Injection

Compound of formula (I)	1-40 mg
Buffer	to pH ca 7
Co-Solvent	to 5 ml

- 5 Buffer : Suitable buffers include citrate, phosphate, sodium hydroxide/hydrochloric acid.

Solvent : Typically water but may also include cyclodextrins (1-100 mg) and co-solvents such as propylene glycol, polyethylene glycol and alcohol.

Tablet

10 Compound	1 - 40 mg
Diluent/Filler *	50 - 250 mg
Binder	5 - 25 mg
Disintegrant *	5 - 50 mg
Lubricant	1 - 5 mg
15 Cyclodextrin	1 - 100 mg

* may also include cyclodextrins

Diluent : e.g. Microcrystalline cellulose, lactose, starch

- 20 Binder : e.g. Polyvinylpyrrolidone, hydroxypropymethylcellulose

Disintegrant : e.g. Sodium starch glycollate, crospovidone

Lubricant : e.g. Magnesium stearate, sodium stearyl fumarate.

Oral Suspension

25 Compound	1 - 40 mg
Suspending Agent	0.1 - 10 mg
Diluent	20 - 60 mg
Preservative	0.01 - 1.0 mg
Buffer	to pH ca 5 - 8
30 Co-solvent	0 - 40 mg
Flavour	0.01 - 1.0 mg
Colourant	0.001 - 0.1 mg

- Suspending agent : e.g. Xanthan gum, microcystalline cellulose
Diluent : e.g. sorbitol solution, typically water
Preservative : e.g. sodium benzoate
Buffer : e.g. citrate
5 Co-solvent : e.g. alcohol, propylene glycol, polyethylene glycol, cyclodextrin

The invention is further illustrated by the following non-limiting examples :

Preparation 1

10 2-(2-Hydroxyethyl)-1-ethoxycarbonylpiperidine

To a stirred solution of 2-(2-hydroxyethyl)piperidine (27.4g, 0.212 mole) in dry dichloromethane (370 ml) containing triethylamine (29.55 ml, 0.212 mole) at 0°C under nitrogen was added dropwise, ethyl chloroformate (20.27 ml, 0.212 mole) in dry dichloromethane (30 ml). After stirring at room temperature overnight dilute HCl (200
15 ml, 1N) was added and the organic phase separated off. The aqueous phase was further extracted with dichloromethane (2 x 50 ml), the combined organic extracts dried (K₂CO₃) and evaporated to give the **title compound** as an oil which was used without further purification.

20 Preparation 2

1-*tert*-Butoxycarbonyl-2-(2-hydroxyethyl)piperidine

2-(2-Hydroxyethyl)piperidine (12.22g, 95mmol) was dissolved in dichloromethane (100ml) at room temperature and stirred under nitrogen. A solution of di-*t*-butyl dicarbonate (20.47g, 94 mmole) in dichloromethane (50ml) was added dropwise over 45
25 minutes. The resulting yellow solution was stirred at room temperature for a further one hour and the dichloromethane then evaporated off to produce a yellow liquid. This material was further evaporated under high vacuum at 50°C to remove *t*-butanol. The yellow oil produced (21.6g) was free of *t*-butanol by N.m.r. and was used without further purification.

30

Preparation 3

1-*tert*-Butoxycarbonyl-4-(2-hydroxyethyl)piperidine

Substituting 4-(2-hydroxyethyl)piperidine (21.7g, 0.176 mole) for 2-(2-hydroxyethyl)piperidine and using the corresponding molar proportions of the other
35 reagents in the method of preparation 2 gave the **title compound** as a straw coloured viscous oil (36.96g) which was used without further purification.

Preparation 4**1-*tert*-Butoxycarbonyl-3-hydroxymethylpiperidine**

Substituting 3-hydroxymethylpiperidine (19.23g, 0.176 mole) for 2-(2-hydroxyethyl)piperidine and using the corresponding molar proportions of the other reagents in the method of preparation 2 gave the **title compound** as a straw coloured viscous oil (36.96g) which was used without further purification.

Example 1**a) 2-[2-(2-Dibenzofuranyloxy)ethyl]-1-ethoxycarbonylpiperidine**

The product of Preparation 1 (4.0g, 20mM), 2-hydroxydibenzofuran (3.67g, 20mM) and triphenylphosphine (5.21g, 20mM) were dissolved with stirring under nitrogen in dry dichloromethane (100ml). The mixture was cooled in an ice-bath and diethylazodicarboxylate (3.46g, 20mM) added dropwise in dichloromethane (20ml). The resulting clear red-brown solution was stood at room temperature for three days and evaporated to dryness to give a sticky brown solid. This material was chromatographed on silica gel using dichloromethane as eluant. Fractions were monitored by t.l.c. and appropriate fractions combined and evaporated to give the **title compound** as a brown oil (6.1g). Mass Spectrum (M+H = 368)
¹H N.m.r. (CDCl₃) δ: 1.15 (3H, t), 1.35-1.75 (7H, m), 1.94 (1H, m), 2.30 (1H, m), 2.90 (1H, t), 3.98-4.20 (4H, m), 4.50 (1H, m), 6.95-7.15 (1H, m), 7.25-7.57 (5H, m), 7.81-7.93 (1H, m).

b) 2-[2-(2-Dibenzofuranyloxy)ethyl]piperidine hydrochloride

The product of Example 1a (6.0g, 16.03 mmole) was dissolved in glacial acetic acid/hydrogen bromide (20ml, 45w/v, excess). The solution was stood at room temperature for two hours and heated on a steam-bath for three hours. The material was then cooled, poured onto water and the aqueous phase basified with 50% NaOH. The mixture was extracted with dichloromethane (X2) and the combined organic extracts washed (water, brine), dried (MgSO₄) and evaporated to give an oil (4.44g). This material was purified by flash chromatography on silica gel. Product was eluted in CH₂Cl₂/2% methanol (the methanol containing 10% .88NH₄OH) and finally CH₂Cl₂/5% methanol. Fractions containing required material were combined and evaporated to dryness to give an oil (2.60g). Some of this material (300mg) was dissolved in ethyl acetate, excess

ethereal HCl (1M) added, the solution concentrated to a low volume and cooled. The **title compound** separated as white crystals (270mg), M.P. 172-174°C. (Mass Spec M+H=296) ($C_{19}H_{21}NO_2HCl \cdot 0.2H_2O$) requires: C, 68.0%, H, 6.7%, N, 4.2%.
found: C, 67.9%; H, 6.6%; N, 4.1%

5

Example 2

a) 2-(2-[3,4-Dichlorophenoxy]ethyl)-1-*tert*-butoxycarbonyl piperidine

Using the product of Preparation 2 (4.55g, 20mM), the conditions of Example 1a, and replacing 2-hydroxydibenzofuran with 3,4-dichlorophenol (3.24g, 20mM), together with
10 corresponding molar proportions of the other reagents gave the **title compound** as a colourless oil (6.48g), (Mass Spec=M+H=375).

1H N.m.r. ($CDCl_3$) δ : 1.38 (9H, s), 1.5-1.9 (8H, m), 2.15-2.30 (1H, m), 2.70-2.88 (1H, m), 3.50-4.10 (2H, m), 4.40-4.55 (1H, m), 6.70 (1H, d of d), 6.90-7.01 (1H, m), 7.21-7.31 (1H, m).

15

b) 2-[2-(3,4-Dichlorophenoxy)ethyl]piperidine hydrochloride

The product of Example 2a (6.0g, 16mM) was dissolved in dichloromethane (80ml) and stirred at room temperature under nitrogen. A solution of trifluoroacetic acid (7.5ml) in dichloromethane (20ml) was added dropwise over 10 minutes and the colourless solution
20 stirred for a further 2 hours. The mixture was evaporated and 2N. NaOH (100ml) added to the oily residue to produce a white, oily solid. This was extracted with dichloromethane (X2) and the combined organic extracts washed (H_2O , brine), dried (Na_2SO_4) and evaporated to dryness to leave a colourless oil (3.53g). A portion of this material (0.825g) was dissolved in ethyl acetate and excess ethereal HCl (1M soln) added to the warm
25 solution. On slow cooling the **title compound** crystallised as white crystals (0.861g), M.P.: 158-159°C. (Mass Spec M+H: 274).
($C_{13}H_{17}Cl_2NO$, HCl) requires: C, 50.3%; H, 5.8%; N, 4.5%
found: C, 50.0%; H, 5.7%; N, 4.3%.

30 Example 3

a) 2-[2-(4-Benzylphenoxy)ethyl]-1-*tert*-butoxycarbonyl piperidine

Replacing the 3,4-dichlorophenol with 4-benzylphenol (3.67g, 20mM) in the method of Example 2a gave the **title compound** as an oil (6.82g). (Mass Spec M+H=396).

b) 2-[2-(4-Benzylphenoxy)ethyl]piperidine hydrochloride

Replacing the product of Example 2a with the product of Example 3a (6.7g, 17mM) in the method of Example 2 and using corresponding molar proportions of the other reagents gave title compound (free base form) as a colourless oil (3.49g). This material was dissolved in ethyl acetate and excess ethereal HCl (1M) added to the stirred solution. A white solid appeared after about one minute which was collected, washed with ethyl acetate/ether to give the **title compound** (3.72g), M.P.: 168-170°C.
(C₂₀H₂₅NO. HCl. 0.2H₂O) requires: C, 71.6%; H, 7.9%; N, 4.2%; Cl⁻, 10.6%.
Found C, 71.5%; H, 7.6%; N, 4.3%; Cl⁻, 10.9%.

Example 4**a) 2-[2-(4-Benzyloxyphenoxy)ethyl]-1-tert-butoxycarbonyl piperidine**

Replacing the 3,4-dichlorophenol with 4-benzyloxyphenol (4.0g, 20mM) in the method of Example 2a gave the **title compound** as an oil (6.97g).
N.m.r (CDCl₃) δ: 1.39 (9H, s), 1.50-1.73 (6H, m), 1.75-1.90 (1H, m), 2.12-2.30 (1H, m), 2.71-2.87 (1H, t), 3.80-4.10 (3H, m), 4.40-4.54 (1H, m), 4.98 (2H, s), 6.75-6.93 (4H, m), 7.28-7.45 (5H, m).

b) 2-[2-(4-Benzyloxyphenoxy)ethyl]piperidine hydrochloride

Replacing the product of Example 2a with the product of Example 4a (6.85g, 16.7mM) in the method of Example 2 and using corresponding molar proportions of the other reagents gave the title compound as the free base (4.80g). This material was dissolved in ethyl acetate and excess ethereal HCl added. A white solid precipitated which was collected, washed with cold ethyl acetate and ether and dried (4.05g). This material was crystallised from methanol/ethyl acetate to give the **title compound** as a white crystalline solid (3.43g), M.P. 215-216°C.
(C₂₀H₂₅NO₂. HCl) requires: C, 69.0%; H, 7.5%; N, 4.0%; Cl⁻, 10.2%.
Found: C, 69.1%; H, 7.5%; N, 4.1%; Cl, 10.0%

Example 5**a) 2-[2-(4-Phenoxyphenoxy)ethyl]-1-tert-butoxycarbonyl piperidine**

Replacing the 3,4-dichlorophenol with 4-phenoxyphenol (1.86g, 10mM) and using corresponding molar proportions of the other reagents in the method of Example 2a gave the **title compound** as an oil (3.28g).

N.m.r. (CDCl_3) δ : 1.38 (9H, s), 1.51-1.70 (6H, m), 1.77-1.91 (1H, m), 2.15-2.31 (1H, m), 2.73-2.88 (1H, t), 3.85-4.10 (3H, m), 4.45-4.57 (1H, m), 6.78-7.05 (6H, m), 7.24-7.34 (3H, m).

5 **b) 2-[2-(4-Phenoxyphenoxy)ethyl]piperidine hydrochloride**

Replacing the product of Example 2a with the product of Example 5a (3.2g, 8.06mM) in the method of Example 2 and using corresponding molar proportions of the other reagents gave the title compound as the free base (2.35g, oil). This material was dissolved in ethyl acetate, the solution warmed on a water-bath and ethereal HCl (1M) added in excess. On cooling a copious white solid separated which was collected, washed with ether and dried to give the **title compound** (1.70g), M.P. = 175°-176°C.

($\text{C}_{19}\text{H}_{23}\text{NO}_2 \cdot \text{HCl}$) requires: C, 68.4%; H, 7.2%; N, 4.2%; Cl^- , 10.6%

Found: C, 68.1%; H, 7.2%; N, 4.2%; Cl^- , 10.3%

15 **Example 6**

a) 2-[2-(2-Benzylphenoxy)ethyl]-1-*tert*-butoxycarbonyl piperidine

Replacing the 4-phenoxyphenol with 2-hydroxydiphenylmethane (1.835g, 10mM) in the method of Example 5a gave the **title compound** as an oil (2.42g).

N.m.r. (CDCl_3) δ : 1.38 (9H, s), 1.50-1.69 (6H, m), 1.75-1.90 (1H, m), 2.10-2.27 (1H, m), 2.72-2.86 (1H, t), [3.95 (s), 3.82-4.08 (m), 5H], 4.38-4.50 (1H, s), 6.75-6.88 (2H, m), 7.00-7.30 (7H, m).

b) 2-[2-(2-Benzylphenoxy)ethyl]piperidine hydrochloride

Replacing the product of Example 2a with the product of Example 6a (2.36g, 6mM) in the method of Example 2 and using corresponding molar proportions of the other reagents gave the free base of the title compound as a colourless oil (1.67g). This was dissolved in ethyl acetate, the solution warmed on a water-bath and ethereal HCl (1M) added in excess. Slow cooling gave the **title compound** as a white crystalline solid (1.49g), M.P. = 115°-117°C.

($\text{C}_{20}\text{H}_{25}\text{NO} \cdot \text{HCl}$) requires: C, 71.6%; H, 7.9%; N, 4.2%; Cl^- , 10.6%.

Found: C, 71.1%; H, 7.6%; N, 4.2%; Cl^- 10.9%

Example 7

a) 4-[2-(3,4-Dichlorophenoxy)ethyl]-1-*tert*-butoxycarbonylpiperidine

35 Using the product of preparation 3 (7.40g, 0.032 mole), the conditions of

Example 2a, and the corresponding molar proportions of the other reagents and recrystallising the product from hexane gave the **title compound** (6.52g) as white needles, m.p. 73-74°C

5 **b) 4-[2-(3,4-Dichlorophenoxy)ethyl]piperidine hydrochloride**

Replacing the product of Example 2a with the product of Example 7a (3.0g, 0.008 mole) in the method of Example 2 and using the corresponding molar proportions of the other reagents gave the **title compound** as the free base (2.75g). This material was dissolved in ethyl acetate and excess ethereal HCl added. A white solid precipitated which was
10 collected, and recrystallised from ethyl acetate to give the **title compound** as white needles (2.17g), M.P. 180-1°C. (Mass Spec M^+ = 274)
($C_{13}H_{17}Cl_2NO \cdot HCl \cdot 0.2H_2O$) requires: C, 49.62%, H, 5.89%, N, 4.45%, Cl, 33.80%
Found: C, 49.38%, H, 5.55%, N, 4.47%, Cl, 34.05%.

15 **Example 8**

a) 4-[2-(4-Benzyloxyphenoxy)ethyl]-1-tert-butoxycarbonylpiperidine

Substituting 4-benzyloxyphenol (4.36g, 0.022 mole) for 3,4-dichlorophenol and using the corresponding molar proportions of the other reagents in the method of Example 7a gave the **title compound** as a white low melting solid (4.71g) which was used without further
20 purification.

b) 4-[2-(4-Benzyloxyphenoxy)ethyl]piperidine hydrochloride

Replacing the product of Example 2a with the product of Example 8a (4.5g, 0.011 mole) in the method of Example 2 and using the corresponding molar proportions of the other
25 reagents gave the **title compound** as the free base. This material was dissolved in ethyl acetate and excess ethereal HCl added. A white solid precipitated which was collected, and recrystallised from ethyl acetate to give the **title compound** as white needles (2.14g),
M.P. 183-4°C. (Mass Spec M^+ = 312)
($C_{20}H_{25}NO_2 \cdot HCl \cdot 0.33H_2O$) requires: C, 67.87%, H, 7.59%, N, 3.95%, Cl, 10.01%
30 Found: C, 67.98%, H, 7.22%, N, 4.03%, Cl, 9.83%.

Example 9

a) 4-[2-(4-Benzylphenoxy)ethyl]-1-tert-butoxycarbonylpiperidine

Substituting 4-benzylphenol (4.05g, 0.022 mole) for 3,4-dichlorophenol and using the
35 corresponding molar proportions of the other reagents in the method of Example 7a gave

the **title compound** as a colourless oil (5.71g) which was used without further purification.

b) 4-[2-(4-Benzylphenoxy)ethyl]piperidine hydrochloride

- 5 Replacing the product of Example 2a with the product of Example 9a (3.6g, 0.0091 mole) in the method of Example 2 and using the corresponding molar proportions of the other reagents gave the **title compound** as the free base. This material was dissolved in ethyl acetate and excess ethereal HCl added. A white solid precipitated which was collected, and recrystallised from acetonitrile to give the **title compound** as white needles (1.49g),
10 M.P. 153-4°C. (Mass Spec M+H = 296)
(C₂₀H₂₅NO.HCl 0.1H₂O) requires: C, 71.98%, H, 7.91%, N, 4.19%, Cl, 10.62%
Found: C, 71.76%, H, 7.71%, N, 4.26%, Cl, 10.79%.

Example 10

- 15 **a) 3-(4-Benzyloxyphenoxyethyl)-1-tert-butoxycarbonylpiperidine**

Using the product of preparation 4 (10.0g, 0.046 mole), the conditions of Example 2a, and the corresponding molar proportions of the other reagents gave the **title compound** (15.54g).

- 20 **b) 3-(4-Benzyloxyphenoxyethyl)piperidine hydrochloride**

Replacing the product of Example 2a with the product of Example 10a (15.54g, 0.038 mole) in the method of Example 2 and using the corresponding molar proportions of the other reagents gave the **title compound** as the free base. This material was dissolved in ethyl acetate and excess ethereal HCl added. A white solid precipitated which was
25 collected, and recrystallised from ethanol to give the **title compound** as white needles (6.30g), M.P. 220-2°C. (Mass Spec M⁺ = 297)
(C₁₉H₂₃NO₂.HCl) requires: C, 68.36%, H, 7.25%, N, 4.20%, Cl, 10.62%
Found: C, 67.94%, H, 7.06%, N, 4.07%, Cl, 10.88%.

- 30 **Example 11**

a) 3-(4-Benzylphenoxyethyl)-1-tert-butoxycarbonylpiperidine

Substituting 4-benzylphenol (8.47g, 0.046 mole) for 4-benzyloxyphenol, and using the corresponding molar proportions of the other reagents in the method of Example 10a, gave the **title compound** (20.5g).

35

b) 3-(4-Benzylphenoxyethyl)piperidine hydrochloride

Replacing the product of Example 2a with the product of Example 11a (20.5g) in the method of Example 2 and using the corresponding molar proportions of the other reagents gave the title compound as the free base. This material was dissolved in ethyl acetate and excess ethereal HCl added. A white solid precipitated which was collected, and recrystallised from acetonitrile to give the **title compound** as white needles (6.96g), M.P. 247-8°C. (Mass Spec M+H = 282)
(C₁₉H₂₃NO.HCl) requires: C, 71.80%, H, 7.61%, N, 4.41%.
Found: C, 71.85% H, 7.57 N, 4.44%.

10

Example 12**a) 2-[4-Benzylphenoxyethyl]-N-methylpiperidine oxalate**

1-Methyl-2-piperidinemethanol (2.58g, 20mM), 4-benzylphenol (3.68g, 20mM) and triphenylphosphine (5.21g, 20mM) were dissolved with stirring under nitrogen in dry dichloromethane (100ml). The solution was cooled in an ice-bath and diethylazodicarboxylate (3.46g, 20mM) in dry dichloromethane (20ml) was added dropwise. The mixture was stood at room temperature for 24 hours, concentrated to about half the volume and chromatographed on silica gel using CH₂Cl₂ as initial eluent followed by CH₂Cl₂/2% MeOH (MeOH contains 10% NH₄OH). Fractions were monitored by t.l.c. and appropriate fractions combined and evaporated to give a white solid. This solid was treated with diethyl ether, some insoluble material (Ph₃P = O) removed and the ether evaporated and the residue re-dissolved in ethyl acetate. A solution of 1 equivalent of oxalic acid dihydrate in ethyl acetate was added to produce a white precipitate. Methanol was added to the hot mixture to produce a clear solution, from which **title product** crystallised on standing. (1.0g), M.P. = 107-109°C.
(C₂₀H₂₅NO, C₂H₂O₄) requires C, 68.5%, H, 7.1%, N, 3.6%
Found C, 68.2%, H, 6.9%, N, 3.6%

20
25**b) 2-[4-Benzylphenoxyethyl]piperidine hydrochloride**

The product of Example 12a (0.5g) was converted to free base (equilibration between N. NaOH and CH₂Cl₂ - organic layer dried, washed and evaporated), producing a colourless oil which was dissolved in toluene (10ml). To the stirred solution at room temperature under argon was added dropwise a solution of 1-chloromethyl chloroformate (0.28g, excess) in dry toluene (5ml). The mixture was heated at reflux temperature for 4 hours, concentrated almost to dryness, methanol (20ml) added and the mixture heated again at reflux temperature for 2 hours. The solvent was evaporated off to produce an oil which

30
35

solidified on standing. The material was crystallised from ethyl acetate/methanol to produce the **title compound** (0.21g) as a white solid, M.P. 95-97°C.

(C₁₉H₂₃NO. HCl) requires C, 71.8%, H, 7.6%, N, 4.4.%

Found C, 71.4%, H, 7.4%, N, 4.5%

5

Example 13

a) 2-[4-Benzyloxyphenoxymethyl]-N-methylpiperidine hydrochloride

Substituting 4-benzyloxyphenol (4.0g, 20mM) for 4-benzylphenol in the method of Example 12a and using identical reaction conditions gave an oil (4.82g) following the chromatography step. This oil was dissolved in ethyl acetate and excess ethereal HCl added. The mixture was evaporated to dryness and the residue crystallised from ethyl acetate/methanol to give the **title compound** as a white solid (3.79g), M.P. 83-85°C.

(C₂₀H₂₅NO₂. HCl, 0.5H₂O) requires C, 67.3%, H, 7.6%, N, 3.9%

Found C, 67.4%, H, 7.4%, N, 4.2%

15

b) 2-[4-Benzyloxyphenoxymethyl]piperidine hydrochloride

Substituting the product of Example 13a (2.27g) for the product of Example 12a in the method of Example 12 and using corresponding molar proportions of the other reagents gave a white solid (3.5gms) after the methanol treatment. This material was re-crystallised from ethyl acetate/methanol to give the **title compound** (1.65g) as white crystals (M.P. =178-179°C)

(C₁₉H₂₃NO₂. HCl) requires C, 68.4%, H, 7.2%, N, 4.2%

Found C, 67.8%, H, 7.0%, N, 4.2%

Example 14

a) (S)-2-[4-Benzylphenoxymethyl]-N-methylpyrrolidine oxalate

Substituting (S)-(-)-1-methyl-2-pyrrolidinemethanol (2.3g, 20mM) for 1-methyl-2-piperidinemethanol in the method of Example 12a and using identical reaction conditions gave a pale-green oil (2.8g) following the chromatography step. Part of this material (1.47g) was dissolved in ethyl acetate and to the hot solution was added a solution of oxalic acid dihydrate (0.66g, 1eq) in methanol. The solution produced was concentrated and refrigerated overnight to give the **title compound** (1.4g) as a colourless, crystalline solid (M.P. 99-100°C).

(C₁₉H₂₃NO. C₂H₂O₄) requires C, 67.9%, H, 6.8% N, 3.8%

Found C, 67.8%, H, 6.7%, N, 3.8%

35

b) (S)-2-[4-Benzylphenoxyethyl]pyrrolidine hydrochloride

- Substituting the product of Example 14a (2.0g) for the product of Example 12a in the method of Example 12 and using corresponding molar proportions of the other reagents gave an oil after the methanol treatment stage. This oil was converted to free base (equilibration between N. NaOH and CH₂Cl₂ etc) and the resulting oil chromatographed on silica gel using CH₂Cl₂/2% MeOH (MeOH contains 10-% NH₄OH) as eluting solvent. An initial product eluted (1.6g) and was shown (N.M.R.) to be unreacted starting material. The eluent was changed to CH₂Cl₂/5% MeOH to yield a second product as an oil (0.62g). This material was dissolved in ethyl acetate/methanol, the solution treated with ethereal HCl, concentrated and refrigerated overnight. The **title compound** crystallised as a buff-coloured solid (0.47g), M.P. 148-150°C.
- C₁₈H₂₁NO. HCl) requires C, 71.2%, H, 7.3%, N, 4.6%
Found C, 70.8%, H, 7.3%, N, 4.6%

15 Example 15**a) 2-[2-(4-Benzoylphenoxy)ethyl]-1-tert-butoxycarbonyl piperidine**

- Substituting 4-hydroxybenzophenone (2.94g, 14.9mM) for 3,4-dichlorophenol in the method of Example 2a and using corresponding molar proportions of the other reagents gave the **title compound** as a colourless oil (3.03g) following column chromatography in dichloromethane.
- ¹H N.M.R. (CDCl₃) δ: 1.38 (9H, s), 1.6-1.8 (6H, m), 1.8-2.0 (1H, m), 2.2-2.4 (1H, m), 2.75-2.9 (1H, m), 3.95-4.15 (3H, m), 4.45-4.6 (1H, m), 6.9 (2H, d), 7.25-7.9 (8H, m).

b) 2-[2-(4-Benzoylphenoxy)ethyl]piperidine hydrochloride

- Substituting the product of Example 15a (3.0g) for the product of Example 2a in the method of Example 2 and using corresponding molar proportions of the other reagents gave a colourless oil (1.98g) following the basification/extraction step. This oil was dissolved in ethyl acetate and the solution treated with ethereal/HCl to produce a white precipitate. This was dissolved by adding methanol, the solution was concentrated and on refrigeration, the **title compound** separated as white crystals (1.32g), M.P. 208-210°C (C₂₀H₂₃NO₂. HCl) requires C, 69.5%, H, 7.0%, N, 4.1%
Found C, 69.2%, H, 6.9%, N, 4.1%

Example 16**a) 2-[2-(3-Benzoylphenoxy)ethyl]-1-tert-butoxycarbonyl piperidine**

Substituting 3-hydroxybenzophenone (2.0g, 10mM) for 3,4-dichlorophenol in the method of Example 2a and using corresponding molar proportions of the other reagents gave the **title compound** as a colourless oil (3.43g) following column chromatography in dichloromethane.

^1H N.M.R. (CDCl_3 δ : 1.37 (9H, s), 1.6-1.8 (6H, m), 1.8-2.0 (1H, m), 2.15-2.35 (1H, m), 2.7-2.9 (1H, m), 3.9-4.1 (3H, m), 4.4-4.6 (1H, m), 7.05-7.15 (1H, m), 7.25-7.65 (6H, m), 7.75-7.85 (2H, d of d)

b) 2-[2-(3-Benzoylphenoxy)ethyl]piperidine hydrochloride

Substituting the product of Example 16a (1.07g, 2.23mM) for the product of Example 2a in the method of Example 2 and using corresponding molar proportions of the other reagents gave a colourless oil (0.64g) following the basification step. This oil was dissolved in ethyl acetate and the solution treated with ethereal HCl to produce on standing a white solid. The material was re-crystallised from acetonitrile to produce the **title compound** as a white solid (0.31g), M.P. 106-108°C

($\text{C}_{20}\text{H}_{23}\text{NO}_2 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$) requires C, 68.5%, H, 7.0%, N, 4.0%

Found C, 68.1%, H, 6.8%, N, 4.2%

Example 17**(+)-2-(2-[4-Benzylphenoxy]ethyl)piperidine hydrochloride**

The product of Example 3 was converted to free base in the usual way (equilibration between N. NaOH and CH_2Cl_2) to produce an oil (1.75g, 5.92mM). This oil was dissolved in ethyl acetate (15ml) and S-(+)-mandelic acid (0.9g, 5.92mM) in ethyl acetate (15ml) added. On refrigeration crystals separated and were collected (2.31g). This material was crystallised five times from ethyl acetate/methanol (monitored by chiral HPLC) to give a white solid (0.83g). Conversion to free base in the usual way gave an oil (0.56g). This was dissolved in ethyl acetate and the solution treated with ethereal HCl.

On cooling the **title compound** separated as white crystals (0.51g), M.P. = 170-171°C.

Specific Rotation = $[\alpha]^{20}_{\text{D}} = +7.70^\circ$. Enantiomeric Purity = 98.6%.

($\text{C}_{20}\text{H}_{25}\text{NO} \cdot \text{HCl} \cdot 0.6\text{H}_2\text{O}$) requires C, 70.1%, H, 8.0%, N, 4.1%, Cl^- , 10.4%

Found C, 70.1%, H, 7.5%, N, 4.2%, Cl^- , 10.6%.

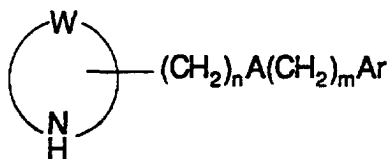
Example 18**(-)-2-(2-[4-Benzylphenoxy]ethyl)piperidine hydrochloride**

The combined mother liquors from all the crystallisations of the mandelic acid salt in Example 17 were converted to free base in the usual way to give an oil (1.19g). This material was dissolved in methanol/ethyl acetate heated to boiling and a solution of R-(-)-mandelic acid (0.62g, 1 equiv) in methanol was added. The slightly cloudy solution was filtered, concentrated and slowly cooled to give white crystals (0.91g). This material was twice re-crystallised from methanol/ethyl acetate to give a white crystalline solid (0.73g). Conversion to free base in the usual way gave a colourless oil (0.58g). This oil was dissolved in ethyl acetate and the solution treated with ethereal HCl. The mixture was refrigerated until the **title compound** separated as a white crystalline solid (0.47g), M.P. = 169-170°C, Specific Rotation = $[\alpha]_D^{20} = -7.26^\circ$. Enantiomeric Purity = 99.7% (C₂₀H₂₅NO. HCl. 0.4 H₂O) requires C, 70.8%, H, 8.0%, N, 4.1%, Cl⁻, 10.5% Found C, 70.8%, H, 7.6%, N, 4.2%, Cl⁻, 10.5%

15

Claims

1. Use of a compound of formula (I):



Formula (I)

in which

W is $-(CH_2)_4$, $(CH_2)_5$, $-(CH_2)_2O(CH_2)_2$ or $-(CH_2)_2S(CH_2)_2$

n is 0 to 6;

m is 0 to 3;

- 10 A is a bond, $-CH=CH-$, $-C\equiv C-$, oxygen, sulphur or NR^1 ;

R^1 is hydrogen, C_{1-8} alkyl or phenyl C_{1-4} alkyl; and

Ar is aryl or heteroaryl, each of which may be optionally substituted;

or a pharmaceutically acceptable salt thereof as a therapeutic agent.

15

2. Use of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of disorders where a calcium channel antagonist is indicated.

20

3. Use according to claim 2 wherein the disorder is a condition or disease related to an accumulation of calcium in the brain cells of mammals.

4. Use according to any of claims 1 to 3 of a compound of formula (I) wherein W represents $(CH_2)_4$, or $(CH_2)_5$.

25

5. Use according to any of claims 1 to 4 of a compound of formula (I) wherein the group $-(CH_2)_nA(CH_2)_mAr$ is α to the ring nitrogen atom.

6. Use according to any of claims 1 to 5 of a compound of formula (I) wherein the length of the chain $-(CH_2)_nA(CH_2)_m$ is from 2 to 6 atoms.

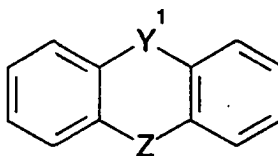
30

7. Use according to any of claims 1 to 6 of a compound of formula (I) wherein A is oxygen or a bond.

8. Use according to any of claims 1 to 7 of a compound of formula (I) wherein Ar represents a phenyl ring substituted by one or two substituents selected from phenyl, phenyl(C₁₋₄)alkyl, phenoxy, benzoyl or phenylC₁₋₄alkoxy group; or by two chloro atoms.

5

9. Use according to any of claims 1 to 7 of a compound of formula (I) wherein Ar represents a tricyclic ring system of the structure :



10 wherein Y¹ represents Y(CH₂)_r, Y is O, S or NR³ (where R³ is hydrogen or C₁₋₄alkyl), Z is (CH₂)_q or -CH=CH-, q is 0, 1 or 2 and r is 0 or 1, or is a corresponding dehydro ring system.

10. Use according to any of claims 1 to 3 of a compound of formula (I) wherein W is (CH₂)₅, the substituent -(CH₂)_nA(CH₂)_mAr is α to the ring nitrogen atom, A is oxygen, n is 1 or 2, m is zero and Ar is phenyl substituted by one of benzyl, benzoyl, phenoxy or benzyloxy, or by two chloro atoms, or Ar is dibenzofuranyl.

11. A method of treatment of a condition or disease caused or exacerbated by the accumulation of calcium in the brain cells of a mammal which comprises administering to a subject in need thereof an effective amount of a compound of formula (I) as defined in any of claims 1 to 10 or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

13. A compound of formula (I) wherein W is -(CH₂)₄ and the group -(CH₂)_nA(CH₂)_mAr is α to the pyrrolidine nitrogen atom, or a salt thereof.

14. A compound of formula (I) wherein Ar is a phenyl group substituted by benzoyl, or a salt thereof.

15. A compound according to claim 14 wherein W is (CH₂)₅, A is oxygen, n is 1 or 2 and m is zero, or a salt thereof.

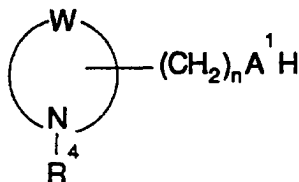
35

16. A compound of formula (I) selected from :

- 2-[2-(4-benzyloxyphenoxy)ethyl]piperidine ,
 2-[2-(4-phenoxyphenoxy)ethyl]piperidine,
 5 2-[2-(2-benzylphenoxy)ethyl]piperidine,
 4-[2-(3,4-dichlorophenoxy)ethyl]piperidine,
 4-[2-(4-benzyloxyphenoxy)ethyl]piperidine,
 4-[2-(4-benzylphenoxy)ethyl]piperidine,
 3-(4-benzyloxyphenoxymethyl)piperidine,
 10 3-(4-benzylphenoxymethyl)piperidine,
 2-[4-benzylphenoxymethyl]piperidine,
 2-[4-benzyloxyphenoxymethyl]piperidine,
 (S)-2-[4-benzylphenoxymethyl]pyrrolidine,
 2-[2-(3-benzoylphenoxy)ethyl]piperidine,
 15 2-[2-(4-benzoylphenoxy)ethyl]piperidine,
 (+)-2-(2-[4-benzylphenoxy]ethyl)piperidine,
 (-)-2-(2-[4-benzylphenoxy]ethyl)piperidine,
 or a salt thereof.

20 17. A process for the preparation of a novel compound of formula (I) which comprises:

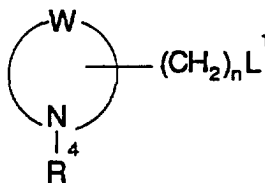
(a) for compounds of formula (I) in which A is O, S or NR¹, reaction of a compound of formula (II):



25 **Formula (II)**

in which W and n are as described for formula (I), A¹ is O, S or NR¹, and R⁴ is an N-protecting group with a compound of formula L(CH₂)_mAr in which m and Ar are as described for formula (I), and L is a leaving group;

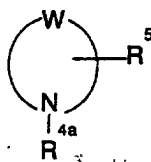
(b) for compounds of formula (I) in which A is O, S or NR¹, reaction of a
 30 compound of formula (III):



Formula (III)

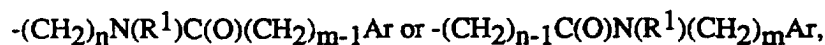
in which W, n and R⁴ are as described above and L¹ is a group displaceable by a nucleophile, with a compound of formula HA¹(CH₂)_mAr where m and Ar are as described for formula (I) and A¹ is as described for formula (II); or

(c) for compounds of formula (I) in which A is NR¹, reduction of a compound of formula (IV) :



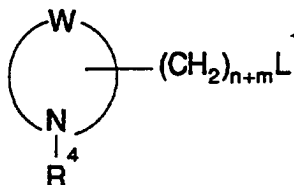
Formula (IV)

10 in which R⁵ represents the group



R^{4a} is hydrogen or an N-protecting group, and W, n, m, and Ar are as described above.

15 (d) for compounds of formula (I) in which A is a bond, reaction of a compound of formula (V) :



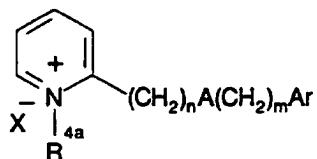
Formula (V)

(wherein W, R⁴, L¹, m and n are as hereinbefore defined);

20

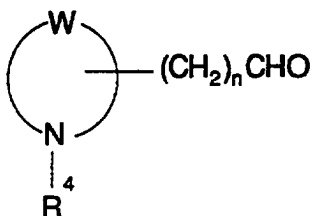
with a compound of formula X¹Ar in which Ar is as described for formula (I), and X¹ is an alkali metal;

(e) For compounds where W is (CH₂)₅ and A is O, S, NR¹ or a bond, reduction of a compound of formula (VI):

**Formula (VI)**

wherein A, Ar m and n are as hereinbefore defined, R^{4a} is hydrogen or an N-protecting group and X⁻ is a counter ion;

- 5 (f) For compounds wherein A is -CH=CH-, reaction of a compound of formula (VII) :

**Formula (VII)**

- 10 (wherein W, R⁴ and n are as hereinbefore defined) with a reagent serving to introduce the group Ar;

- (g) Interconversion of one compound of formula (I) to a different compound of formula (I), e.g. the reduction of a compound wherein A is -CH=CH- to a compound wherein A is -CH₂-CH₂- or reduction of a benzoyl substituent in the group Ar to a benzyl group;
- 15 followed where necessary by removal of the N-protecting group R⁴, and optionally thereafter forming a salt.

INTERNATIONAL SEARCH REPORT

International Application No.

PC1/EP 93/03473

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 A61K31/445 A61K31/40 C07D211/18 C07D211/22 C07D207/08
C07D265/30 C07D279/12 C07D405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 339 579 (NOVO NORDISK) 2 November 1989 see table 1 see page 3, line 1 - line 51 ---	1-17
P,A	WO,A,92 22527 (SMITHKLINE BEECHAM) 23 December 1992 cited in the application see the whole document ---	1-17
A	WO,A,92 02501 (SMITHKLINE BEECHAM) 20 February 1992 cited in the application see the whole document ---	1-17
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
 "&" document member of the same patent family

Date of the actual completion of the international search

28 March 1994

Date of mailing of the international search report

- 5. 04. 94

Name and mailing address of the ISA

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 Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+ 31-70) 340-3016

Authorized officer

Kissler, B

INTERNATIONAL SEARCH REPORT

International Application No

PC1/EP 93/03473

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 02502 (SMITHKLINE) 20 February 1992 cited in the application see the whole document ---	1-17
P,A	WO,A,93 15052 (SMITHKLINE) 5 August 1993 see the whole document ---	1-17
X	EP,A,0 000 693 (THOMAE) 21 February 1979 see claims 1-9 see example 1 ---	1,6,7
A	EP,A,0 266 574 (A/S FERROSAN) 11 May 1988 see the whole document ---	1-16
X	GB,A,1 319 252 (CIBA-GEIGY) 6 June 1973 see claim 2 see example 1 see page 1, line 42 - line 45 ---	1,4,7,12
X	GB,A,1 203 149 (ICI) 26 August 1970 see examples 1-7 see page 1, line 9 - page 2, line 34 see claim 5 ---	1,4,6-8, 12
X	GB,A,1 096 441 (BRISTOL-MYERS) 29 December 1967 see claims 13-16 see page 1, line 10 - page 3, line 9 see examples 14,22 ---	1,4-8, 10,12
X	US,A,4 822 778 (G. ABERG) 18 April 1989 see claim 1 see example 1 ---	1,4-7,12
X	EP,A,0 012 643 (PHARMINDUSTRIE) 25 June 1980 see abstract ---	1,4,6,7, 12
X	EP,A,0 004 288 (MERCK) 3 October 1979 see examples 2-237 see claims 1,6 ---	1,4-7, 12,13
X	US,A,3 360 526 (W. F. MINOR) 26 December 1967 see claim 1 see examples 4,11 ---	1,4-8, 10,12, 13,16
X	EP,A,0 449 187 (DU PONT MERCK) 2 October 1991 see table 15, examples 287, 288 -----	14,15

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2

INTERNATIONAL SEARCH REPORT

national application No.

PCT/EP 93/ 03473

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compounds/composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims searched completely: 10, 15, 16
./.
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

The notation
"Ar is aryl or heteroaryl" (claim 1)

is inaccurate and thus not admissible.

The definition of the following substituent(s) is too general and/or encompasses too broad a range of totally different chemical groups, only partly supported by examples given in the descriptive part of the application:

W, Ar, A, no point of attachment of the side chain
(including even simple derivatives like Phenylpyrrolidine, phenylpiperidine etc.)

The number of theoretically conceivable compounds resulting from the combination of all claimed substituents of above list precludes a comprehensive search. The generic formula (I) cannot even be searched comprehensively on-line without without going far beyond which can be economically justified. Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been limited to the following case(s):

Piperidines and pyrrolidines having at least one substituent: $(CH_2)_n-A-Ar$
where $n=1-6$, A is O and Ar is phenyl substituted by a member chosen from the group
Cl, $-O-CH_2-Ph$, $-CH_2-O-Ph$, $-CO-Ph$, $-CH_2-Ph$, $-O-Ph$.
(all claims)

For PCT :

(Cf. Arts. 6, 15 and Rule 33 PCT, Guidelines Exam. Part B, Chapt. III, 3.6, 3.7)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/EP 93/03473

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0339579	02-11-89	AU-B- 631121	19-11-92
		AU-A- 3336689	02-11-89
		JP-A- 1313461	18-12-89
		US-A- 5017585	21-05-91
		US-A- 5208232	04-05-93
		US-A- 5158961	27-10-92
		US-A- 5227379	13-07-93
WO-A-9222527	23-12-92	AU-A- 1975092	12-01-93
WO-A-9202501	20-02-92	AU-A- 8324391	02-03-92
		CN-A- 1062349	01-07-92
		EP-A- 0542844	26-05-93
		JP-T- 6500092	06-01-94
WO-A-9202502	20-02-92	AU-A- 8327191	02-03-92
		CN-A- 1061963	17-06-92
		EP-A- 0542846	26-05-93
		JP-T- 6500093	06-01-94
WO-A-9315052	05-08-93	AU-B- 3364493	01-09-93
EP-A-0000693	21-02-79	DE-A- 2728898	18-01-79
EP-A-0266574	11-05-88	AU-B- 602735	25-10-90
		AU-A- 8048287	05-05-88
		DE-D- 3788709	17-02-94
		US-A- 4877799	31-10-89
		US-A- 5017585	21-05-91
		US-A- 5019582	28-05-91
		US-A- 4985446	15-01-91
		US-A- 5208232	04-05-93
		US-A- 5158961	27-10-92
		US-A- 5227379	13-07-93
		JP-A- 63126866	30-05-88
		ZA-A- 8708019	29-04-88
GB-A-1319252	06-06-73	CH-A- 573909	31-03-76
		CH-A- 559173	28-02-75
		BE-A- 751451	04-12-70

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/03473

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-1319252		CA-A- 980783	30-12-75
		DE-A- 2025518	10-12-70
		FR-A, B 2052932	16-04-71
		GB-A- 1319251	06-06-73
		NL-A- 7008158	08-12-70
		US-A- 3853892	10-12-74
		US-A- 3801581	02-04-74
		CH-A- 565761	29-08-75
		CH-A- 556337	29-11-74
CH-A- 566311	15-09-75		

GB-A-1203149	26-08-70	AT-A- 289115	15-02-71
		BE-A- 734296	09-12-69
		CH-A- 513856	15-10-71
		FR-A- 2010615	20-02-70
		NL-A- 6908842	12-12-69
		SE-B- 356978	12-06-73
		US-A- 3634437	11-01-72

GB-A-1096441		DE-A- 1545577	31-07-69
		US-A- 3360526	
		US-A- 3381013	

US-A-4822778	18-04-89	NONE	

EP-A-0012643	25-06-80	FR-A- 2443246	04-07-80
		CA-A- 1137485	14-12-82
		JP-C- 1423356	15-02-88
		JP-A- 55113715	02-09-80
		JP-B- 62030988	06-07-87
		US-A- 4294841	13-10-81

EP-A-0004288	03-10-79	DE-A- 2811952	31-10-79
		AU-A- 4507279	20-09-79
		JP-A- 54132564	15-10-79
		US-A- 4225608	30-09-80

US-A-3360526		DE-A- 1545577	31-07-69
		GB-A- 1096441	
		US-A- 3381013	

formation on patent family members

PC1/EP 93/03473

08-12-92
10-12-92